

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07J 1/00, A61K 31/565	A1	(11) International Publication Number: WO 99/67270 (43) International Publication Date: 29 December 1999 (29.12.99)
(21) International Application Number: PCT/EP99/04101 (22) International Filing Date: 14 June 1999 (14.06.99) (30) Priority Data: 98202051.3 19 June 1998 (19.06.98) EP (71) Applicant (for all designated States except US): AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): LEYSEN, Dirk [BE/BE]; Kerkstraat 26, B-3920 Lommel (BE). VAN DER VOORT, Hendrikus, Adrianus, Antonius [NL/NL]; Esdoornstraat 7, NL-5461 CH Veghel (NL). VAN DER LOUW, Jaap [NL/NL]; Pauwoog 12, NL-5345 EN Oss (NL). (74) Agent: KRAAK, H.; P.O. Box 20, NL-5340 BH Oss (NL).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: CYCLOALKYL-CARBOXYLIC ACID ESTERS OF 7.ALPHA.METHYL-ESTR-4-EN-3-ONE 17.BETA.-OL (19-NOR 7.ALPHA.-METHYLTESTOSTERONE) (57) Abstract The invention is the novel androgen (7 α ,17 β)-17-[[<i>(trans</i> -4-butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one (MENT buccilate) and related cycloalkyl esters. This compound distinguishes favourably from other testosterone derivatives in that it has a good solubility in oily media. It particularly exhibits a good dissolved potency relative to testosterone. The compound is particularly suitable for administration by means of injection.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CJ	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CYCLOALKYL-CARBOXYLIC ACID ESTERS OF 7.ALPHA.METHYL-ESTR-4-EN-3-ONE 17.BETA.-OL (19-NOR 7.ALPHA.-METHYLTESTOSTERONE)

5 The invention is in the field of androgenic hormones, more specifically derivatives of testosterone.

Testosterone derivatives are known. Testosterone itself, the natural male hormone, has many known drawbacks as far as methods of administration are concerned. It has a short-lasting activity, is insoluble in the usual pharmaceutically acceptable media, and is not very potent.

10 The more potent dihydrotestosterone (5 α -reduced form of testosterone) is considered a health-risk, notably for the prostate.

More potent androgens are 7 α -methyl-19-nortestosterone (MENT) and related compounds, such as disclosed in FR 4.521 M and US 5,342,834. However, MENT suffers from a bad

15 solubility and short duration of action.

As androgens having an improved duration of action, the cycloalkyl esters of testosterone have been disclosed in US 4,948,790. These, however, are neither very potent, nor sufficiently soluble, and lead to too low plasma levels of testosterone than are feasible.

20

New androgenic hormones are needed which *inter alia* satisfy the demands connected with new areas of interest, such as male contraception and male HRT (hormone replacement therapy). Thus, *e.g.*, male contraception may comprise a regimen of administration of hormones in which a progestagen serves to achieve a contraceptive effect and an androgen

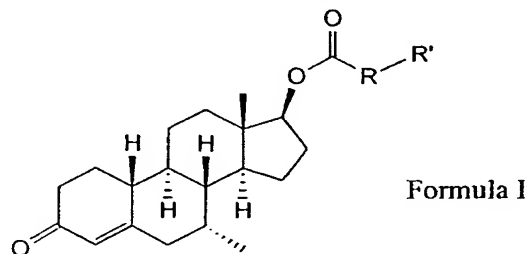
25 serves to supplement the resulting decreased testosterone level. Another option is that male contraception is performed with an androgenic hormone alone. The regular androgen intake needed for this requires androgens which are improved as to potency and duration of action, and for which a practical way of administration is available. As low a frequency of administration being desired, there is a demand for androgens which have such physico-

30 chemical properties as to be rendered into a solution, particularly a solution by which the androgen can be administered via injection, preferably once a week or less frequent, or orally via a capsule to be taken, *e.g.* daily. This means that a basic desired property for a novel

androgen is that it has an improved solubility in one or more pharmaceutically acceptable liquids.

Even more desired is an androgen which has a favourable relationship of potency and solubility, as a weak androgen will require more of it to be dissolved in order to attain the same activity than in the case of a more potent androgen. This means an androgen having an improved relative "dissolved potency", hereinafter referred to as RDP, wherein the RDP of a given androgen in a given medium is the product of its androgenic potency relative to that of the natural male hormone testosterone and its solubility in the medium relative to that of testosterone.

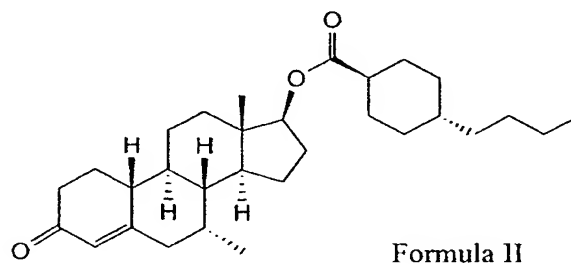
It is an object of the invention to provide an androgenic hormone which satisfies the above demand. According to the invention, this is achieved by a compound of the general formula I



15

wherein R stands for cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and R' is hydrogen or a straight chain or branched chain alkyl group of 2-6 carbon atoms.

In a preferred embodiment, the invention is the compound (7 α ,17 β)-17-[[*(trans*-4-butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, which has the following structural formula II:



This preferred compound of the invention is also to be referred to as 7 α -methyl-19-nortestosterone buciclate, in short MENT buciclate.

- 5 The compounds of the invention have a significantly better solubility than could be expected on the basis of the known testosterone derivatives, including MENT. Moreover, the compounds of the invention have a surprisingly higher RDP than the known compounds.

The compounds of the invention can be prepared by esterification of the 17-OH group of
10 MENT with a suitable carboxylic acid or carboxylic acid derivative, such as, in the case of the preferred compound, *trans*-4-butylcyclohexanecarboxylic acid or derivatives thereof. This esterification may be carried out using methods well known in the art or readily available from the chemical literature, for example, using methods and catalysts described in Advanced Organic Chemistry, J. March, 4th Ed, pages 1281-1282, 1992, or analogously with
15 the compounds disclosed in US 4,948,790. MENT can be prepared as disclosed in FR 4.521 M and US 5,342,834.

The invention also pertains to each of the above compounds, and particularly MENT buciclate, as a medicine. The compounds of the invention being potent androgens, they can
20 be used in, *inter alia*, male contraception and male or female hormone replacement therapy. Thus the invention also pertains to a method of treatment of androgen insufficiency, by administering to a human male or female an effective amount of a compound of the invention, such as MENT buciclate. The invention also is in the use of of a compound of the invention, such as MENT buciclate for the preparation of a medicine for treating androgen
25 insufficiency. In the context of the invention, the term "androgen insufficiency" is to be understood to pertain to all kinds of diseases, disorders, and symptoms in which a male or a female suffers from too low a testosterone level, such as in hypogonadal men. In particular, the androgen insufficiency to be treated by the compound of the invention is the reduction of the testosterone level which a human male incurs as a result of age (the compound of the
30 invention is then used for male hormone replacement therapy), or when he is subject to male contraception. In the context of male contraception, the compound of the invention especially serves to neutralise the effect of regimens of male hormone contraception in which a

sterilitant such as a progestagen or LHRH (luteinizing hormone releasing hormone) is administered regularly, *e.g.* daily, or it is used as the sole male contraceptive substance.

5 The invention also relates to pharmaceutical formulations comprising a compound of the invention, such as MENT buciclate and a pharmaceutically acceptable carrier. Thus the carrier may be in a solid form or liquid form, and the formulation may be an oral dosage unit such as a tablet or, preferably, an oral solution, *e.g.* in a capsule. Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Gennaro *et al*, Remington's Pharmaceutical Sciences, 10 (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). The compound can also be administered via an implant, a patch, or any other suitable device for the sustained release of an androgen composition. The preferred oral dosage unit is that of a capsule containing the compound of 15 the invention taken up in a liquid medium as described below.

In order to benefit most from the compound's androgenic activity, administration of the compound dissolved in an oil is preferred, *i.e.* either orally as above, and notably via (intramuscular) injection. The compounds of the invention, and notably MENT buciclate, 20 have a solubility in oily media, which makes them particularly suitable for a liquid pharmaceutical formulation comprising a compound as defined above, and preferably MENT buciclate, dissolved in a pharmaceutically acceptable oil. Suitable oils are, *e.g.* arachis oil, oleic acid, ricinus oil, sesam oil and the like. Arachis oil is preferred.

25 For injection the preferred injection device is a needleless injection system, *e.g.* as described in US 5,599,302. To this end the compound may also be suspended in an aqueous medium, but the above solutions in oil are preferred. Methods and compositions for making liquids suitable for parenteral administration are known in the art, see *e.g.* Remington's, pages 1545 ff.

30

For oral administration, any capsule made from a pharmaceutically acceptable wall material can be employed. Methods and compositions for making capsules suitable for oral

administration are known in the art, see *e.g.* Remington's, pages 1658 ff. A preferred material is a softgel such as used for Andriol® capsules.

5 The invention also pertains to a method of treatment of androgen insufficiency, by administering to a human male, by injection or by means of an oral dosage unit, an effective amount of MENT buciclate dissolved in a pharmaceutically acceptable oil. The invention also is in the use of MENT buciclate for the preparation of a medicine for treating androgen insufficiency by injecting into a human male an effective amount of MENT buciclate dissolved in a pharmaceutically acceptable oil, or by orally administering such an oily
10 solution.

The dose of and regimen of administration of the compounds as defined above, or a pharmaceutical composition thereof, to be administered will obviously depend on the therapeutic effect to be achieved and will vary with the route of administration, and the age
15 and condition of the individual subject to whom the medicament is to be administered, and/or or the particular contraceptive or HRT regimen in which it is used. Typical doses are 100 mg or more per three months upon intramuscular administration and 50-250 mg, more preferably 80 mg per day upon oral administration.

20 The invention will be further explained hereinafter with reference to the following Examples and Figures.

Figure 1

A graphic representation of the relative "dissolved potency" RDP in arachis oil of
25 testosterone (1), MENT (2), testosterone buciclate (3), and MENT buciclate (4).

Figure 2

A graphic representation of the relative "dissolved potency" RDP in oleic acid of testosterone (1), MENT (2), testosterone buciclate (3), and MENT buciclate (4).

EXAMPLE 1

(7 α ,17 β)-17-[[*(trans*-4-Butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one.

- i) - A total of 8 grams of commercially available *trans*-4-butylcyclohexanecarboxylic acid were added to 9.5 ml of thionyl chloride and the reaction mixture was stirred overnight at ambient temperature. The excess of thionyl chloride was evaporated under reduced pressure to yield 8.80 g of *trans*-4-butylcyclohexanecarbonyl chloride.
- ii) - At 0-5° C, 2.23 g (11 mmol) of this crude *trans*-4-butylcyclohexanecarbonyl chloride were added to a stirred solution of 1.58 g (5.5 mmol) of (7 α ,17 β)-17-hydroxy-7-methylestr-4-en-3-one in 16 ml of pyridine. The reaction mixture was allowed to reach room temperature and was stirred overnight. Thereafter, ice was added and after stirring for another 2 hours, the reaction mixture was poured into ice-water, containing 80 ml of 2 N HCl, followed by ethyl acetate extraction. The organic layers were washed with water, cold 1 N NaOH solution and brine, dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed over silica. Elution with heptane-ethylacetate (4:1) and evaporation gave a crystalline residue. Collection of the crystals yielded 1.4 g of MENT buclate, *i.e.* (7 α ,17 β)-17-[[*(trans*-4-butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, m.p. 66 °C, $[\alpha]_D^{20} = +50^\circ$ (c = 1; dioxane), MS (ESI): 454.

EXAMPLE 2

Following procedures analogous to those described under Example 1, and using (7 α ,17 β)-17-hydroxy-7-methylestr-4-en-3-one and an appropriate (alkyl)cycloalkylcarboxylic acid as starting materials, the following products were prepared:

- a) - (7 α ,17 β)-17-[(Cyclopropylcarbonyl)oxy]-7-methylestr-4-en-3-one, m.p. 98-99 °C.
- b) - (7 α ,17 β)-17-[[*(2*-Hexylcyclopropyl)carbonyl]oxy]-7-methylestr-4-en-3-one (mixture of 2 diastereomers, ratio 2:1), $[\alpha]_D^{20} = +45.0^\circ$ (c = 0.35; dioxane).
- c) - (7 α ,17 β)-17-[(Cyclobutylcarbonyl)oxy]-7-methylestr-4-en-3-one, $[\alpha]_D^{20} = +46.0^\circ$ (c = 1; dioxane).
- d) - (7 α ,17 β)-7-Methyl-17-[[*(3*-pentylcyclobutyl)carbonyl]oxy]estr-4-en-3-one (mixture of 2 diastereomers, ratio 1:1), $[\alpha]_D^{20} = +41.5^\circ$ (c = 0.6; dioxane).
- e) - (7 α ,17 β)-7-Methyl-17-[[*(3*-pentylcyclopentyl)carbonyl]oxy]estr-4-en-3-one (mixture

of 2 diastereomers, ratio 4:1), $[\alpha]_D^{20} = +36.0^\circ$ (c = 0.45; dioxane).

- f) - (7 α ,17 β)-17-[[*(cis*-4-Ethylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one,
m.p. 90 °C.
- g) - (7 α ,17 β)-17-[[*(trans*-4-Ethylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one,
5 m.p. 117-119 °C.
- h) - (7 α ,17 β)-7-Methyl-17-[[*(cis*-4-propylcyclohexyl)carbonyl]oxy]estr-4-en-3-one,
 $[\alpha]_D^{20} = +37.2^\circ$ (c = 0.5; dioxane).
- i) - (7 α ,17 β)-7-Methyl-17-[[*(trans*-4-propylcyclohexyl)carbonyl]oxy]estr-4-en-3-one,
m.p. 89-91 °C.
- 10 j) - (7 α ,17 β)-17-[[*(cis*-4-Butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one,
 $[\alpha]_D^{20} = +40.0^\circ$ (c = 1; dioxane).
- k) - (7 α ,17 β)-17-[[[*(cis*)-4-(1,1-Dimethylethyl)cyclohexyl]carbonyl]oxy]-7-methylestr-
4-en-3-one, m.p. 150 °C.
- l) - (7 α ,17 β)-17-[[[*(trans*)-4-(1,1-Dimethylethyl)cyclohexyl]carbonyl]oxy]-7-methylestr-
15 4-en-3-one, m.p. 132-135 °C.
- m) - (7 α ,17 β)-7-Methyl-17-[[*(cis*-4-pentylcyclohexyl)carbonyl]oxy]estr-4-en-3-one,
 $[\alpha]_D^{20} = +40.0^\circ$ (c = 1; dioxane).
- n) - (7 α ,17 β)-7-Methyl-17-[[*(trans*-4-pentylcyclohexyl)carbonyl]oxy]estr-4-en-3-one,
m.p. 81-83 °C.
- 20 o) - (7 α ,17 β)-17-[[*(cis*-4-Hexylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one,
 $[\alpha]_D^{20} = +37.1^\circ$ (c = 1; dioxane).
- p) - (7 α ,17 β)-17-[[*(trans*-4-Hexylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one,
m.p. 79-82 °C.

25 EXAMPLE 3

(17 β)-17-[[*(trans*-4-Butylcyclohexyl)carbonyl]oxy]androst-4-en-3-one.

The title compound (*i.e.* testosterone buciclate) was prepared from 1.58 g of (17 β)-17-hydroxyandrost-4-en-3-one and 2.23 g of *trans*-4-butylcyclohexanecarbonyl chloride
30 following procedures analogous to those described under Example 1. Yield 1.3 g, m.p. 133°
C, $[\alpha]_D^{20} = +81^\circ$ (c = 1; dioxane), MS (ESI): 454.

EXAMPLE 4

About 20-30 mgs of compound were powdered and then dissolved in as little solvent as necessary to dissolve all the visible particles. Dissolution was accomplished by heating in a waterbath of 50 °C and shaking on a Vortex™ shaker for 15 minutes. The solubility was calculated by determining the amount of compound (in mg) dissolved per ml of solvent. Results are collected in the table below.

COMPARATIVE EXAMPLE

The solubility and the androgenic potency of MENT buccilate and three reference compounds was used to determine RDP. The results are given in the Figures. With regard to clinically desirable anabolic and antigonadotropic effects (androgenic effects), MENT is ten times more potent than testosterone in rats (Kumar N et al, Endocrinology 130: 3677-3683 (1992) and J Steroid Biochem Molec Biol 52: 105-112 (1995)) and monkeys (Cummings D et al, J Clin Endocrinol Metab 83, 4212-4219 (1998)). The RDP is determined as follows:

$$\frac{\text{Solubility of compound}}{\text{Solubility of testosterone}} \times \text{potency of compound relative to that of testosterone}$$

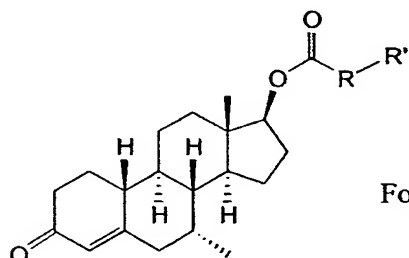
Table. Solubility of testosterone, MENT, testosterone buciclate, and compounds of the invention in arachis oil and in oleic acid.

5	Compound/ Example	solubility in arachis oil (mg/ml)	solubility in oleic acid (mg/ml)
10	testosterone	<< 0.1	~ 25
	MENT	≤ 0.1	~ 15
	testosterone buciclate (Ex. 3) 1-2		~ 50-60
	MENT buciclate (Ex. 1)	~ 10	~ 50
	Example 2a	8	25
15	Example 2b	> 200	> 250
	Example 2c	5	15
	Example 2d	300	160
	Example 2e	> 250	> 200
	Example 2f	50	< 10
20	Example 2g	10	25
	Example 2h	65	< 10
	Example 2i	10	30
	Example 2j	50	100
	Example 2k	15	< 10
25	Example 2l	5	10
	Example 2m	40	100
	Example 2n	15	50
	Example 2o	40	100
30	Example 2p	10	30

From the table it can be learned that the solubility of MENT buciclate and the other compounds of the invention in arachis oil is much better than that of testosterone, MENT, and testosterone buciclate. The solubility of MENT buciclate and most of the other compounds of the invention in oleic acid is also better than expected in view of that of the known androgens.

Claims

1. A compound of the structural formula I:



Formula I

- 5 wherein R stands for cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and R' is a hydrogen or a straight chain or branched chain alkyl group of 2-6 carbon atoms.
2. The compound (7 α ,17 β)-17-[[*(trans*-4-butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one (MENT buclate).
- 10 3. A compound of the structural formula I as a medicine.
4. MENT buclate as a medicine.
- 15 5. The use of a compound of the structural formula I for the preparation of a medicine for treating androgen insufficiency.
6. The use of MENT buclate for the preparation of a medicine for treating androgen insufficiency.
- 20 7. A pharmaceutical formulation comprising a compound of the structural formula I and a pharmaceutically acceptable carrier.
8. A pharmaceutical formulation comprising MENT buclate and a pharmaceutically acceptable carrier.
- 25 9. A pharmaceutical formulation according to claim 7 or 8, characterised in that the carrier is a liquid in which MENT buclate is dissolved.

10. A kit for male contraception comprising means for the administration of a progestagen and means for the administration of an androgen, characterised in that the latter means is a pharmaceutical formulation according to claim 7 or 8.

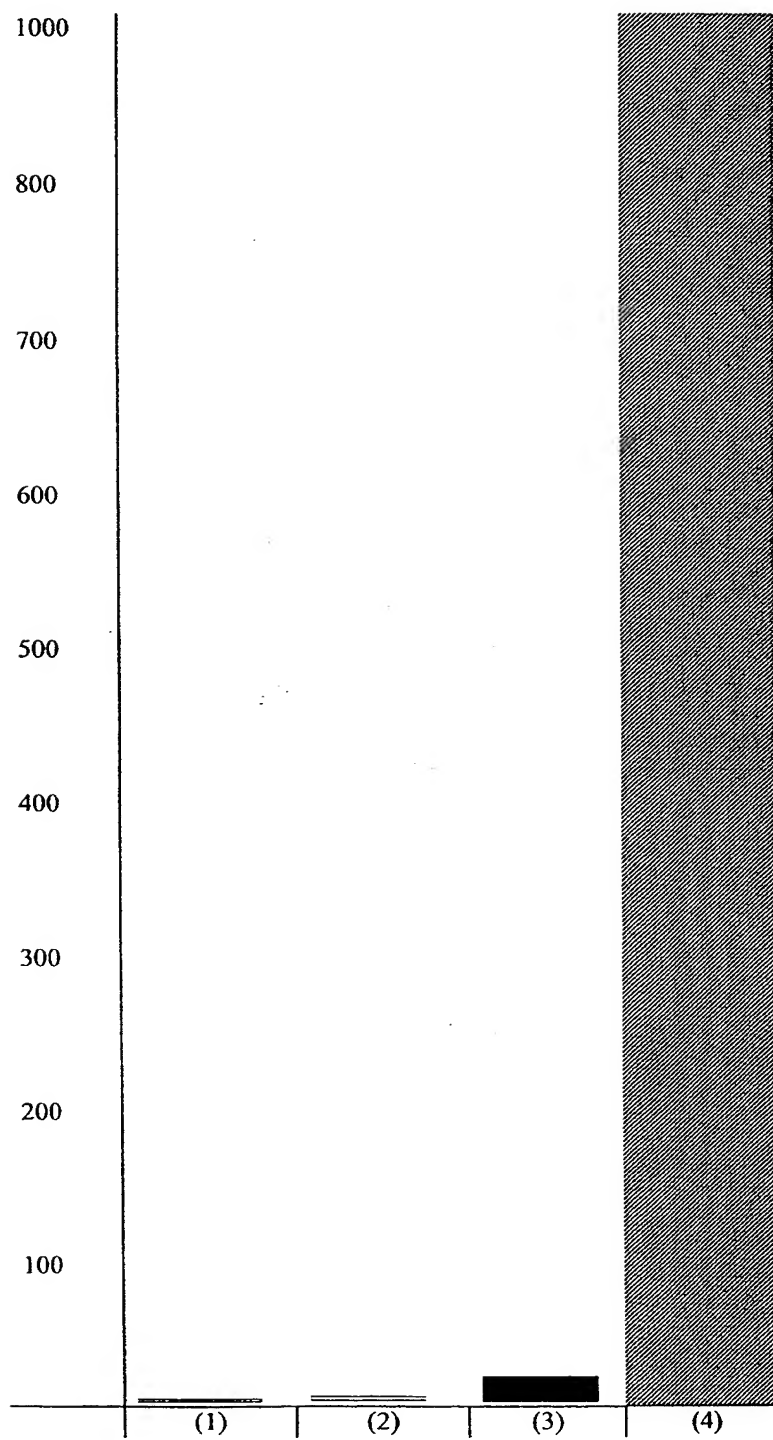


FIG.1

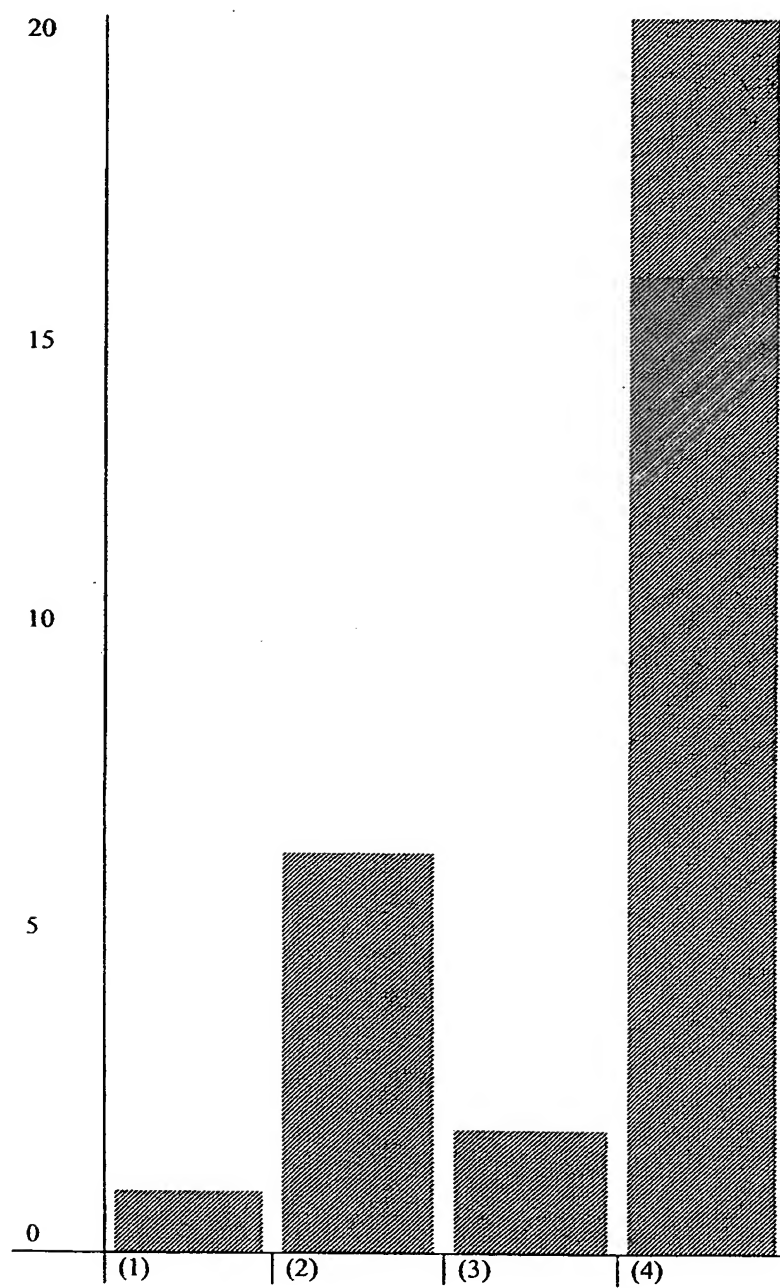


FIG.2

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04101

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07J1/00 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUNT W L ET AL: "Sexual activity in castrated male rabbits after oral administration of 7.alpha.-methyl-19-nortestosterone 17-(1-adamantoate)" PHYSIOLOGY AND BEHAVIOR, vol. 11, no. 6, 1973, pages 893-896, XP002082863 the whole document	1-10
Y	US 5 342 834 A (BARDIN C WAYNE ET AL) 30 August 1994 (1994-08-30) cited in the application column 2, line 11 - line 20 column 2, line 39 - line 40 -/--	1-10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

14 September 1999

Date of mailing of the international search report

27/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Watchorn, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/04101

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 948 790 A (ARCHER SYDNEY ET AL) 14 August 1990 (1990-08-14) cited in the application column 2, line 18 - line 32; examples I, III, IV column 2, line 65 - line 68 -----	1-10
Y	RAJALAKSHMI M ET AL: "Effect of two new androgen esters on serum levels of testosterone in castrated rhesus monkey" CONTRACEPTION, vol. 42, no. 2, 1990, pages 235-240, XP002082864 the whole document -----	1-10
Y	MATLIN, S. A. ET AL: "Long-acting androgens: analytical and preparative HPLC of testosterone esters" JOURNAL OF HIGH RESOLUTION CHROMATOGRAPHY AND CHROMATOGRAPHY COMMUNICATIONS., vol. 10, no. 4, April 1987 (1987-04), pages 186-190, XP002115189 DR. ALFRED HUETHIG VERLAG. HEIDELBERG., DE ISSN: 0935-6304 the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04101

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5342834 A	30-08-1994	NONE	
US 4948790 A	14-08-1990	NONE	